REMARKS

By the foregoing amendments, claim 110 has been amended. Support for the amendment to claim 110 can be found in the specification at page 15, lines 14-19 and 23; page 4, lines 10-18; Example 1; and page 16, lines 2-8. Claims 110-114 are pending in the application. Support for the amendments to the specification can be found throughout the specification and in the claims.

Informalities in the Specification

The Examiner notes that the replacement pages submitted for pages 20-22 have ribose rings that are in L configuration rather than D, as provided elsewhere in the specification. Submitted herewith are new replacement pages 20-22 which have ribose rings of unspecified D or L configuration. On page 19 of the specification, a sentence has been added to indicate that all ribose rings in Schemes 1-4 contain D rings.

The Examiner also notes structure errors at the bottom of page 14. These errors are corrected in the foregoing amendments to the specification.

The Rejections under 35 USC § 112, First Paragraph

Claims 110-114 stand rejected under Section 112, first paragraph, as lacking adequate written description in the specification.

Specifically, claim 110, lines 8-9, are rejected as allegedly too functional because the term "opening the epoxide ring if said universal solid support is structure (I') to generate structure (I)" fails to list reagents used in the ring opening. The foregoing amendments are believed to address this issue. The amendments find support in the specification at page 9, lines 25-34; and page 16, lines 2-8. As is discussed at page 9, lines 25-34, it is convenient to open the epoxide ring during the standard detritylation step of solid phase oligonucleotide synthesis employing anhydrous acidic conditions. Generally anhydrous, acidic or basic conditions in the presence of HNu can be used, as being well known in the art to be useful for epoxide ring opening.

The Examiner also rejects claims 110-114 as non-enabled for modified supports wherein the residue which links the terminal epoxide or hydroxy/"Nu" moiety, is entirely organic, i.e., contains only C and H. The Examiner may also be rejecting the

specification as non-enabling for complete removal of the phosphate from the final oligonucleotide using a basic or nucleophilic reagent.

By the foregoing amendments, claim 110 has been amended to recite that the hydrocarbyl radical is linked to the organic or inorganic polymer by an amide or ether linkage. Support for this amendment can be found in the specification at page 15, lines 14-24 (amide linkage) and Example 1 (ether linkage). Further, support can be found on page 4, lines 10-18, wherein it is taught that methods are known for synthesizing a column bearing hydrocarbyl radicals with NH_2 and/or COOH groups. Thus, Applicants have clarified that the residue between the polymer and the hydrocarbyl – (epoxide or hydroxyl/"Nu") moiety is not entirely made only of H and C. Page 10 of the specification has been amended to clarify this point as well. Support for the amendment to page 10 can be found at page 15, lines 14-24 and Example 1.

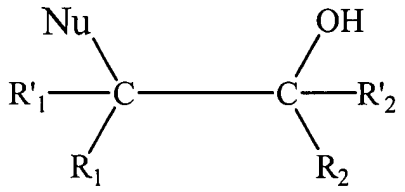
The Examiner alleges that there is no exemplification in support of the claims. Actually, Example 1 illustrates a hydrocarbyl-glycidyloxy moiety, i.e., structure (I'), linked via an ether linkage to an inorganic/organic polymer. Although the amide linkage between hydrocarbyl-hydroxyl/Nu moiety and polymer may not be exemplified, its synthesis is described on page 15, lines 14-24.

In regard to the possible non-enablement rejection relating to removal of the phosphate from the final oligonucleotide, Applicant submits that this step is adequately supported by the specification. Claim 110 presently recites in step (f) that the oligonucleotide is cleaved "from the support by adding a base or nucleophile resulting in intramolecular nucleophilic displacement, whereby the cleaved oligonucleotide has a free 5' or 3'OH." Support for this language can be found in the specification at page 6, lines 15-22; page 7, lines 1-8; and page 13, line 14 to page 14, line 6. Applicants respectfully submit that the Examiner has not provided any evidence that would contradict Applicants' teaching in the specification that the methods for final deprotection can be used to separate the oligonucleotide from the support such that the phosphate group is left on the support. Absent such evidence, Applicants' objective teaching must be taken as true (*In re Marzocchi*, 169 USPQ 367 (CCPA 1971)).

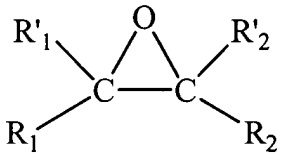
In view of the foregoing, Applicants respectfully request withdrawal of the foregoing Section 112, first paragraph rejections.

The Examiner cautions that an amendment to address the Section 112, first paragraph rejection may result in imposition of another Section 102 rejection over Webb et al., U.S. 4,659,774. Applicants respectfully submit that the amendments made herein to claim 110 do not render this claim anticipated by the '774 patent. The '774 patent describes a polymer-linker for use in oligonucleotide synthesis (see cols. 3-4). In one embodiment, the polymer has oxirane moieties, which are attacked by a linker group with amines at either end. One of the linker group amines serves as the nucleophile to open the oxirane moiety and create a compound in which one of the amines of the linker is covalently attached to a carbon which is adjacent to the carbon with the resulting hydroxy group. The resulting compound is referred to in Webb et al. as a polymer support/linker. This compound is subsequently coupled to a nucleoside by reacting nucleoside-pentachlorophenyl succinate with the polymer support/linker, whereby the free amine of the linker displaces the pentachlorophenyl on the succinate (col. 4, lines 7-15). Thus, the first nucleoside monomer is conjugated to the support via 2 linkers: $H_2N-(CH_2)_a-X-(CH_2)_b-Y-(CH_2)_c-NH_2$ and succinate.

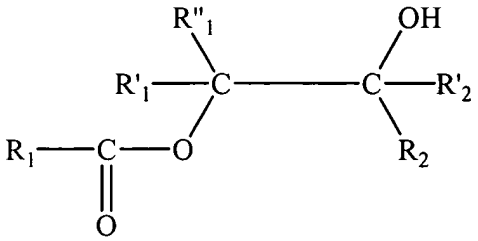
In contrast, the subject amended claims are directed to a method of polynucleotide synthesis in which the polymer is in one of R_1, R'_1, R''_1, R_2, and R'_2 in one of the following structures:



(I),



(I'),



(II),

The first nucleotide monomer binds via its 3' or 5' phosphate group to, in the case of structures (I) or (II), the OH on the carbon adjacent to the carbon bearing the Nu or carboxy group. In the case of structure (I'), the epoxide ring is first opened to generate a hydroxy to which the first monomer becomes attached.

One advantage of the subject method relative to Webb et al. is that the subject method provides a universal solid support to which the first and subsequent monomers are added, wherein the universal solid support has a structure that makes it possible for detachment of the finished oligonucleotide by intramolecular nucleophilic displacement (see page 13, line 14 to page 15, line 2 of the specification). In contrast, Webb et al. provide a support with two linkers and a nucleoside, upon which subsequent steps of oligonucleotide synthesis proceed. The Webb support is not universal in the sense that the first nucleoside must be attached to the support-first linker with a succinate linker. Further, the resulting polymer-linker-linker-nucleoside of Webb et al. is not designed to undergo intramolecular nucleophilic displacement upon complete oligonucleotide synthesis.

The universal support of the subject method also has the advantage of permitting the use of the same monomer reagent and reaction conditions for the very first base as for all subsequent bases (page 6, lines 23-29, and page 7, line 32 to page 8, line 1 of the specification). In contrast, the first monomer of Webb is a nucleoside attached to a pentachlorophenyl succinate and may be considered to be part of the support (col. 4, lines 7-11).

In view of these differences between the claimed method and the method described in Webb et al., it is submitted that the subject claimed invention is novel and non-obvious over the '774 patent.

The Rejections under 35 USC § 112, Second Paragraph

Claims 110 and 113 stand rejected under Section 112, second paragraph as allegedly indefinite.

Specifically, claim 110, step (b) recites "opening the epoxide ring" without listing reagents or reactants. By the foregoing amendments, reagents have been added to the step (b).

Further claim 113 recites structure (II'b), which has no antecedent basis. By the foregoing amendment, (II'b) has been corrected to (I'b).

It is therefore respectfully requested that the Section 112, second paragraph rejections be withdrawn.

Closing Remarks

It is believed that the foregoing amendments and remarks bring the subject case into condition for allowance and notification of same is respectfully requested. If the Examiner believes that a phone conference would expedite prosecution, he is invited to phone the undersigned at 303-268-0066.

It is believed that no fees are due with this submission. If this is in error, please charge any necessary fees to Deposit Account No. 19-5117.

Respectfully submitted,

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Feb 20, 2004

cc: B. Sauerbrei
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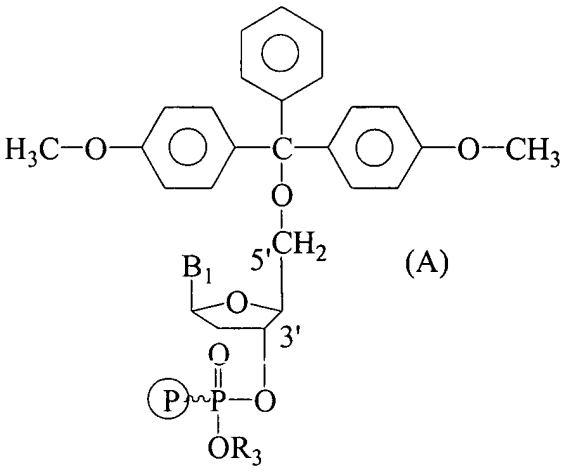
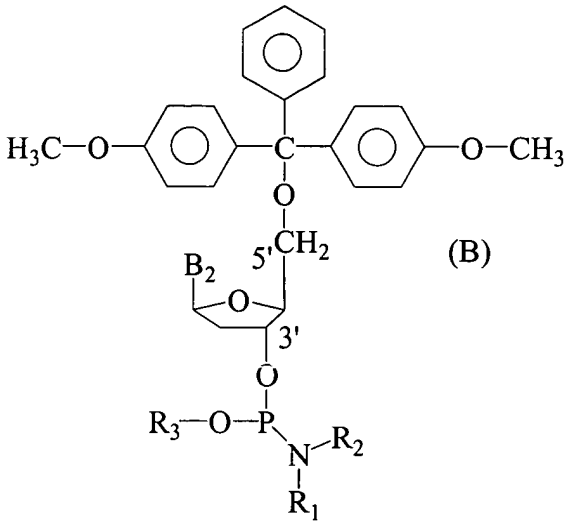
Nucleoside attached to the support:

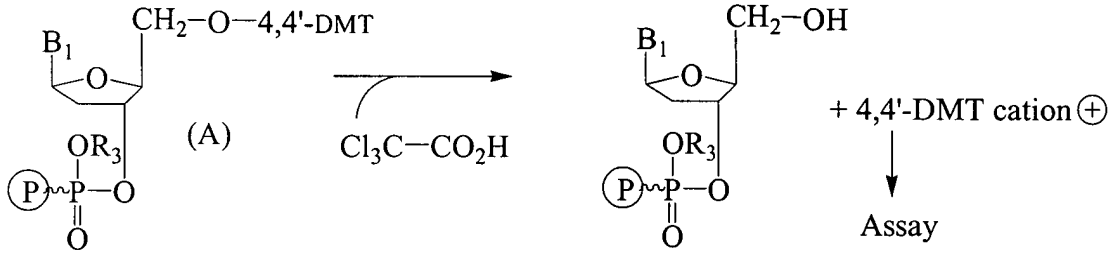


(A)

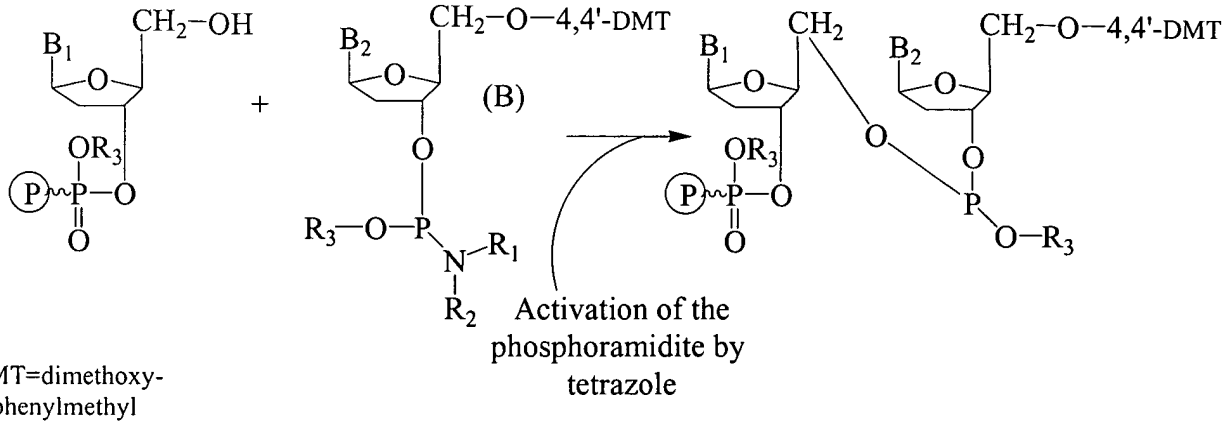
Phosphoramidite:



(B)



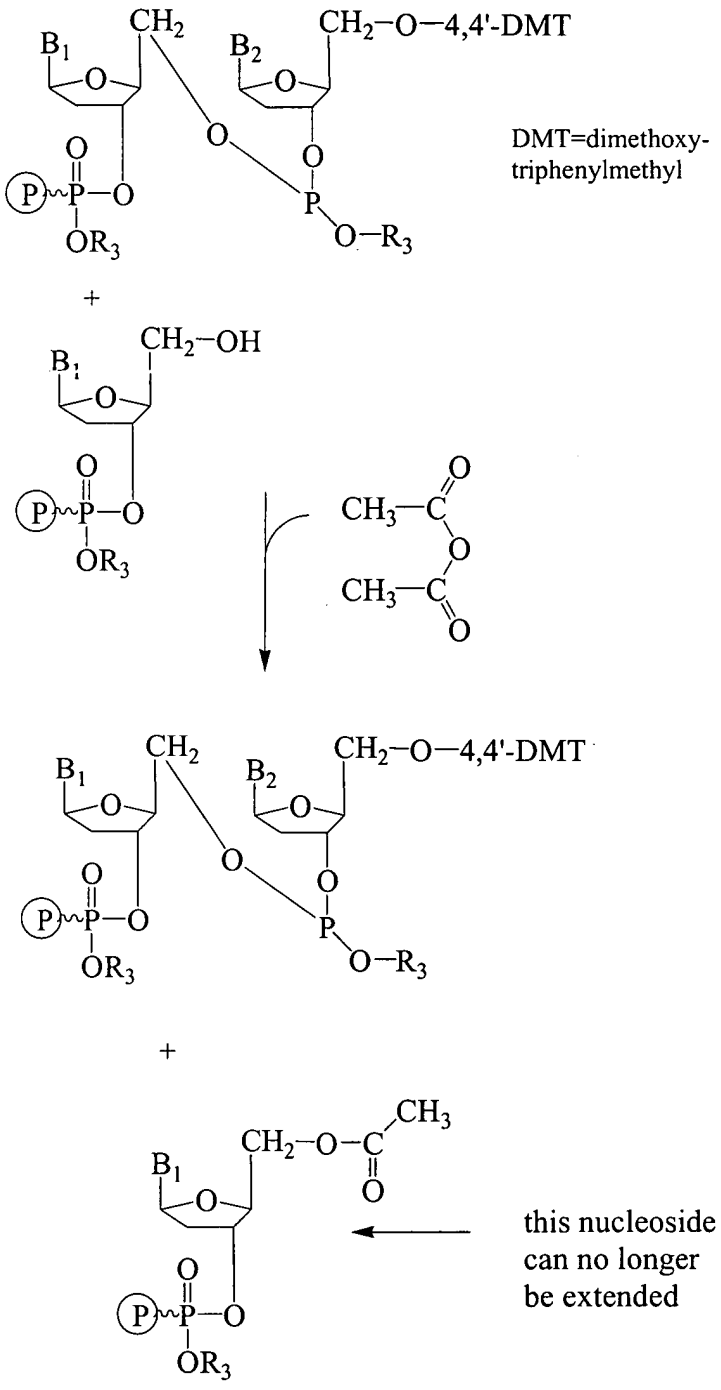
Scheme 1



DMT=dimethoxy-triphenylmethyl

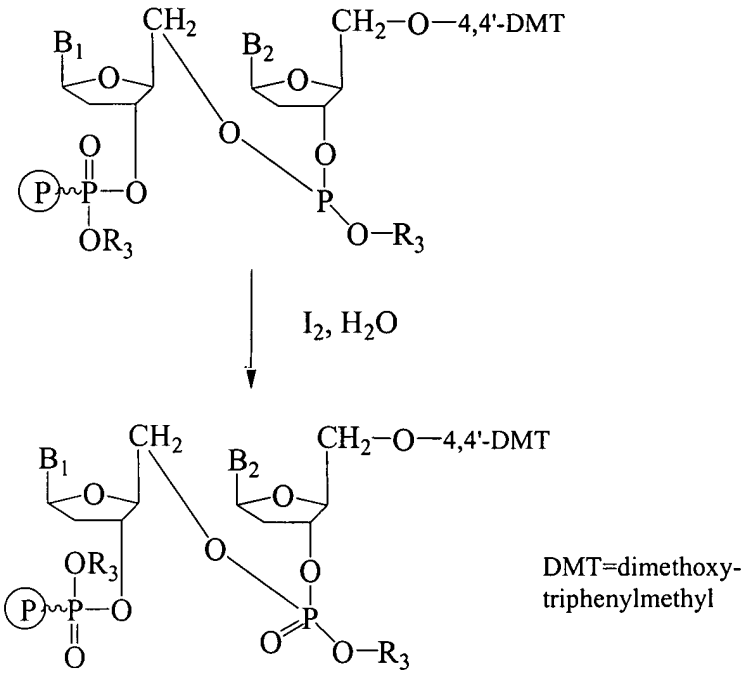
Scheme 2

2) Capping:



Scheme 3

3) Oxidation:



Scheme 4

EXAMPLE 1

1 g of porous glass powder (CPG 00350C®; f; CPG Inc. USA) in 5 ml of a 10% solution of 3-glycidyloxypropyltrimethoxysilane

$$[(Me\text{-}O)_3 - Si - (CH_2)_3 - O - CH_2 - \underset{\diagup \quad \diagdown}{CH} - CH_2]$$

in acetonitrile, the mixture is left standing for 30 minutes at a temperature of 50°C and the support is then separated out by filtration, washed with acetonitrile (3X5 ml) and dried under vacuum.

The number of oxy groups is determined, after opening of the epoxide ring, by means of the reaction of dimethoxytrityl chloride in pyridine followed by absorption spectrophotometric measurement of the trityl cation in a mixture of perchloric acid and ethanol at 495 nm. A capacity of 50-100 micromol per 1 g of support is obtained.